TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

EXECUTIVE SUMMARY

Background

Transmission electron microscopy (TEM) is the preferred analytical method for measuring asbestos concentrations in ambient atmospheres. The absence of a standard protocol for TEM analysis and the discovery and refinement of new techniques have resulted in a variety of procedures which may not necessarily provide comparable estimates of airborne asbestos concentration. An important difference between protocols is the use of direct and indirect transfer techniques. The direct transfer method was developed primarily to estimate structure concentration, whereas the indirect transfer method was developed primarily to estimate mass concentration. In a direct transfer the original filter is prepared for analysis with minimal disturbance of the particles upon it. In an indirect transfer, the particles are removed from the original filter and resuspended on a second filter prior to microscopic examination. Although the original spatial distribution of the particles is lost, indirect transfer is thought to provide greater control over analytical precision through improved distribution of materials over the surface of the filter.

Early TEM measurements of airborne asbestos used an indirect transfer method and expressed the results in terms of mass (ng/m^3). Fiber concentrations were not reported because it was thought that the indirect transfer technique might have broken up larger asbestos structures and artificially inflated the fiber count. The U.S. Environmental Protection Agency (EPA) has used the indirect transfer technique for many of its research programs, in part to overcome the problem of non-asbestos debris in some sampling situations, and in part because the type of filter most suited for direct transfer (polycarbonate) was thought to be more difficult to handle and transport in the field. However, improvements in the direct transfer technique applied to mixed cellulose filters have made direct transfer a feasible option.

Prior to carrying out a recent study of airborne asbestos levels in public buildings (USEPA 1988), EPA convened a meeting of microscopists and other asbestos measurement experts to determine the most appropriate analytical protocol. A direct transfer method using mixed cellulose ester filters was selected. A similar TEM protocol was later specified under the Asbestos Hazard Emergency Response Act (AHERA) to determine when an asbestos work site is sufficiently clean for the containment barriers to be removed.

To investigate the relationship between airborne asbestos levels measured by the two transfer techniques and possibly provide a basis for comparison with earlier studies based on indirect transfer, a subset of the samples collected in the 1988 EPA study were reanalyzed using an indirect transfer method. This document reports the results of the EPA analysis and extends the discussion to include data from six other studies.

Results and Conclusions

The investigation confirmed the generally held opinion that the direct and indirect transfer methods provide different estimates of airborne asbestos concentration. There is insufficient information, however, to determine the mechanisms responsible for the difference and thereby recommend one method over the other. The specific conclusions are listed below followed by recommendations for further research.

- **TEM analysis of air samples using indirect transfer methods tends to provide estimates of total airborne asbestos structure concentration that are higher than those obtained using direct transfer methods.** This conclusion is consistent with general opinion and implies that airborne asbestos levels estimated by one method are not directly comparable to those estimated by the other.

  Evidence. A review of available data (seven studies) revealed this relationship in every study despite variations in sampling, analytical, and counting protocols.

- **There is no single factor that can be applied to convert measurements made using an indirect transfer method to a value that is comparable with measurements made using a direct transfer method.** The quantitative relationship between estimates obtained by the two transfer methods is expected to depend on sampling and analytical protocols as well as the nature of the asbestos structures in the air.

  Evidence. In the studies considered here, measurements made by the indirect transfer method were 3.8 times to 1,700 times higher than measurements made by the direct transfer method. The highest value of 1,700 was estimated from a set of 45 samples collected in a school district. The lowest value of 3.8 was obtained in an interlaboratory study of 12 samples of amphibole.

- **Provided a single method is applied consistently, the choice of method is not as critical when measurements are to be used only for comparative purposes (for example, comparison of airborne asbestos levels inside and outside an abatement site). When measurements are to be interpreted in relation to a fixed standard, the choice of method is more important.**

  Evidence. Both methods appear to detect changes in airborne asbestos concentrations. Although the relationship between the two methods is not strong, higher concentrations determined from one method tend to correspond to higher levels obtained by the other. A statistically significant relationship of this type was found between measurements made by the two transfer methods in all seven studies. In a study designed to compare indoor and outdoor airborne asbestos levels, the same trend was revealed by both methods.

- **Based on data from the studies considered in this report, it seems unlikely that the larger airborne asbestos concentrations estimated by the indirect transfer method can be explained solely by breakdown of large asbestos structures into smaller components.** Alternative hypotheses involving interference by debris and association of unattached structures may also be important.

  Evidence. In the two studies for which data are readily available, the indirect transfer method counted more structures than the direct transfer method in all size categories. One would expect to count fewer large structures with the indirect transfer method if larger asbestos structures were being broken down into smaller ones.

Additional Research

The information needed to select the appropriate protocol for a given situation could be obtained with a relatively modest research program. A series of studies is suggested to:

- Further investigate structure size distributions for direct and indirect TEM preparations in order to distinguish among alternative hypotheses and thereby determine which method more accurately reflects biologically meaningful airborne asbestos concentrations; and

- Compare the spatial distribution of asbestos structures on samples prepared by direct and indirect transfer methods in order to characterize the precision of each method.

II. CONCLUSIONS AND RECOMMENDATIONS

The results from the recent EPA study (USEPA 1988), together with a review of six other studies in the literature (Tuckfield et al 1988, Lee 1987 (two data sets), Burdett 1985a, Chatfield 1986, and Cook and Marklund 1982) lead to the following conclusions:

- **TEM analysis of air samples using indirect transfer methods tends to provide estimates of total airborne asbestos structure concentration that are higher than those obtained using direct transfer methods.** This conclusion is consistent with general opinion and implies that airborne asbestos levels estimated by one method are not directly comparable to those estimated by the other.

  Evidence. A review of available data (seven studies) revealed this relationship in every study despite variations in sampling, analytical, and counting protocols.

- **There is no single factor that can be applied to convert measurements made using an indirect transfer method to a value that is comparable with measurements made using a direct transfer method.** The quantitative relationship between estimates obtained by the two transfer methods is expected to depend on sampling and analytical protocols as well as the nature of the asbestos structures in the air.

  Evidence. In the studies considered here, measurements made by the indirect transfer method were 3.8 times to 1,700 times higher than measurements made by the direct transfer method. The highest value of 1,700 was estimated from a set of 45 samples collected in a school district. The lowest value of 3.8 was obtained in an interlaboratory study of 12 samples of amphibole.

- **Provided a single method is applied consistently, the choice of method is not as critical when measurements are to be used only for comparative purposes (for example, comparison of airborne asbestos levels inside and outside an abatement site). When measurements are to be interpreted in relation to a fixed standard, the choice of method is more important.**

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to compare indoor and outdoor airborne asbestos levels, the same trend was revealed by both methods.

- **Based on data from the studies considered in this report, it seems unlikely that the larger airborne asbestos concentrations estimated by the indirect transfer method can be explained solely by breakdown of large asbestos structures into smaller components.** Alternative hypotheses involving interference by debris and association of unattached structures may also be important.

  Evidence. In the two studies for which data are readily available, the indirect transfer method counted more structures than the direct transfer method in all size categories. One would expect to count fewer large structures with the indirect transfer method if larger asbestos structures were being broken down into smaller ones.

Selection of an appropriate protocol in a given situation involves consideration of bias (systematic error) and precision (random error). The conclusions above, combined with opinions expressed by microscopists, indicate that the indirect and direct transfer methods differ with respect to bias and precision, but there is insufficient information to recommend one method over the other. The necessary information could be obtained with a relatively modest research program involving the analysis of existing data and experiments designed specifically for this purpose. It is recommended that studies be performed to:

- Further investigate structure size distributions for direct and indirect TEM preparations in order to distinguish among alternative hypotheses and thereby determine which method more accurately reflects biologically meaningful airborne asbestos concentrations; and

- Compare the spatial distribution of asbestos structures on samples prepared by direct and indirect transfer methods in order to characterize this component of precision.

These recommendations are discussed in more detail in Section VI.

VI. DISCUSSION

An analytic method should be sufficiently accurate for its intended purpose. Accuracy has two components: bias and precision. Bias refers to a systematic deviation of the measured value from the true value of the quantity being measured. In this case the objective is to characterize exposure in a biologically meaningful way, that is, in terms of the number and type of structures that are inhaled. Precision refers to the uncertainty associated with repeated measurements of the same quantity. The direct transfer method is often characterized as being less biased than the indirect transfer method, whereas the indirect transfer method is considered more precise by some researchers. Neither of these claims is supported by extensive data. Bias and precision are discussed in turn below, together with suggestions for further research that could assist in selecting the appropriate analytical method for a given situation.

A. Bias

Bias must be considered within the context of the application. If measurements are to be used in a comparative manner (e.g., comparing airborne asbestos levels inside and outside a building), a bias that applies equally to both sets of measurements may not affect the comparison. If, however, the objective is to measure exposure in order to assess risk, a bias may have a significant impact on the interpretation of the data. Although the details are controversial, it is thought that the dimension of asbestos structures is important in determining the incidence of disease. Special attention should be devoted to minimizing bias with respect to asbestos structures that contribute most to disease incidence. (Note that the contribution is determined not only by relative potency of asbestos structures of different sizes, but also by their relative abundances.) An ideal measurement method would mimic the effect of respiration, etc. on complex structures (BCM) so that those that readily disintegrate would be represented by their individual components, while those that are firmly linked would be counted and sized as single structures.

The studies considered in this paper all support the generally accepted belief that airborne asbestos concentrations estimated by an indirect transfer method are larger than those estimated by a direct transfer method. Breakdown of larger structures during the ashing, sonication, and resuspension steps is assumed to be the main explanation for the difference. Fiber size information from Studies 1 and 5, however, does not provide strong support for this hypothesis. Although more small fibers are counted using an indirect transfer method, there is not a corresponding

decrease in the number of large fibers and BCM, nor in the size of the BCM.

Chatfield (1986) provides two additional hypotheses for the larger structure counts obtained with an indirect transfer method. First, with the direct transfer method, structures may be hidden by organic debris. (This hypothesis was also suggested by Sebastien et al, 1984.) The effect is likely to be greatest for small structures, but applies to structures of all sizes. During indirect transfer the debris is removed by ashing, thereby improving visibility and increasing the structure count. Second, with the direct transfer method, small structures loosely associated with larger structures (for example, touching but not bonded) are counted as a single structure. During indirect transfer, these structures are disassociated from the larger structures and are counted as individual structures.

All three mechanisms may play a role to a varying degree under different circumstances. Note that predictions depend on the size distribution of asbestos structures in the sampled air. When only small fibers are present, the breakdown hypothesis would predict little difference between direct and indirect preparations whereas the debris hypothesis would predict higher measurements with the indirect preparation. When the majority of structures are complex, the breakdown hypothesis would predict higher measurements with the indirect preparation whereas the association hypothesis would predict little difference.

Given that measurements by indirect TEM are generally higher than those by direct TEM, it is important to determine whether indirect measurements incorporate a positive bias (because, for example, the additional preparation artificially inflates the number of fibers) or the direct measurements incorporate a negative bias (because, for example, fibers are covered by debris). Fiber size data should be available for Studies 2, 3, and 4, and could be analyzed to distinguish between competing hypotheses. The number of structures counted, particularly those in the larger size categories, could limit the investigation. A designed experiment in which samples were prepared according to carefully specified protocols would provide more conclusive information. Experimental factors include preparation method, filter loading (low to high), and prevalence of complex structures.

B. Precision

Other considerations being equal, the method with the highest precision is preferable. For TEM analysis of airborne asbestos, the spatial distribution of asbestos structures on the surface of a filter is important in determining precision. Only a tiny fraction of the original filter area is examined with the electron microscope. It is assumed that the area is

representative of the entire filter surface in order to estimate the concentration of asbestos in the sampled air. (Other aspects of the protocol including counting rules, filter loading, and area of filter examined also affect precision. These are not discussed further here because they can be varied independently of the transfer method. The effect of procedures such as ashing and resuspension that are uniquely associated with indirect transfer method would be included in any overall study of precision.)

Chatfield (1984, 1986) has argued that the spatial distribution of asbestos structures on the filter is closer to random (i.e., follows a Poisson distribution) when an indirect transfer method is used. If structure counts per grid opening are available for Studies 1, 2, 3 and 4, Chatfield's claim can be tested. Efforts are underway to obtain these data. The question may also be addressed experimentally by preparing samples by both techniques and examining the filter in greater detail than is done during routine analysis. A relatively simple statistical design and analysis would be sufficient to detect marked differences and could provide a definite recommendation. A more sophisticated experiment is needed to explore heterogeneity on various spatial scales in order to determine the advisability of preparing more than one portion of the filter or analyzing multiple grids.

Since breakup of structures (resulting in a positive bias) and uneven spatial distribution of structures on the filter (resulting in decreased precision) are claimed to be the major disadvantages of the indirect and direct transfer methods respectively, further research to support or reject these claims would be a valuable and relatively low cost contribution to the continuing discussion over the choice of analytical protocol.

EXHIBIT S

Expert Report re W R Grace - Related Attic Insulation Asbestos Litigation –

The Biological Relevance of Tremolite Cleavage Fragments.

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Introduction

This report discusses the biological relevance of tremolite cleavage fragments in relation to W R Grace related Attic Insulation asbestos litigation. Various investigations thus demonstrate that a significant proportion of the tremolite found in the airborne dust produced during the manipulation of W R Grace Attic Insulation is not asbestiform but derived from cleavage fragments. In this regard, you have asked me to provide you with an opinion, to a reasonable degree of medical and scientific certainty, as to whether such cleavage fragments can cause asbestos related disease. On the basis of my detailed analysis of the literature, extensive discussions with other experts, and personal experience and knowledge of the mechanisms underlying the production of asbestos related disease and related illnesses as reflected in the appended resume, I can say, to a reasonable degree of scientific and medical certainty, that cleavage fragments cannot contribute to the production of asbestos related disease. The detailed foundation underlying this opinion is set forth below. I reserve the right to supplement this Report and rely upon other Expert Reports should additional relevant information become available.

Personal Experience & Background

- I am a medical doctor, pathologist, basic scientist, and independent consultant toxicologist who specializes in, amongst many other things, the health effects of asbestos and other mineral fibers.

- I have a doctorate of medicine from the Hahnemann Medical Center in Philadelphia, Pennsylvania. I have a Doctorate of Philosophy in zoology and botany from the University of Oxford in Oxford, U.K. as well as a Master of Arts degree denoting Senior Status from the University of Oxford.

- I am licensed to practice medicine and surgery by the State of New York and the Commonwealth of Pennsylvania and was fully registered with the General Medical Counsel in the United Kingdom. I am board certified in Anatomic Pathology by the American Board of Pathology. I am a Diplomate of the National Board of Medical Examiners. I have worked as an Assistant Medical Examiner at the Office of the Medical Examiner of the City of New York and as Pathologist to Her Majesty's Coroner for Oxford (UK). I have also served as a Visiting Pathologist to the Imperial Cancer Research Fund, London (UK) and was an Honorary Member of the Clinical Trials Study Unit to the Imperial Cancer Research Fund, Oxford (UK). I was an Associate Member of the Royal College of Pathology (UK) in Neuropathology.

- I was a Member of the Faculty of Biological Sciences at the University of Oxford and am presently an Adjunct Member of the Childhood Cancer Research Group, Department of Paediatrics, University of Oxford.

- I have been a member of the British Medical Association, the British Society Development Biologists, the International Fibre Safety Group and the British Society of Neuropathologists. I am a member of the American Medical Association and am on the Fiber Subcommittee of the International Commission on Occupational Health.

- I have authored over 40 publications and two textbooks, both as sole author. The Forward to the first book, Ilgren [1993], "Mesotheliomas of Animals, A Compendium of the World's Literature", was written by Dr. J Christopher Wagner, the first person to demonstrate a causal connection between asbestos and mesothelioma. The Forward to the second book, Ilgren [1991a], "Initiation and Promotion of Cancer", was written by Sir Richard Peto, one of the world's leading cancer epidemiologists. Amongst my publications are key articles in the peer-reviewed scientific literature on the health effects of asbestos and other mineral fibers, with particular emphasis on mesothelioma. The mesothelioma textbook and other articles published in conjunction with Dr. Wagner review, amongst other things, the incidence of mesothelioma in untreated animals as well as the incidence seen following exposure to asbestiform fibers, nonasbestiform fibers and many types of nonfibrous agents.

- In my capacity as an independent consultant, pathologist, and toxicologist, I have testified in numerous court proceedings in the United States and the United Kingdom.

- My rate of compensation is $250 per hour for Consultation, $300 per hour for Deposition testimony, and $350 per hour for Trial testimony.

Scientific Report

Cleavage Fragments and Asbestos Fibers Have Fundamentally Different Properties:

- Amphiboles make up as much as 6% of the earth's crust and approximately 30% of the rocks in the continental United States contain amphiboles as major constituents. [Wylie et al, 1985].

- The asbestiform habit is rare; the vast majority of amphibole minerals are nonasbestiform [Wylie et al, 1985; Zoltai, 1979]. Amphibole (nonasbestiform) cleavage fragments and amphibole (asbestiform) asbestos fibers have fundamentally different properties [NRC, 1984; Zoltai, 1979, 1981; Dorling and Zussman, 1987; Walker, 1981]. Since they are nearly identical chemically[1], the main difference between them is their physical appearance.

- Tremolite can be asbestiform or nonasbestiform. Nonasbestiform tremolite is not naturally fibrous but occurs in either a prismatic or an acicular growth habit.

- "Growth habit" refers to the manner in which amphibole crystals grow. The precise determinants of a mineral's growth habit are not known [Zussman pers com, 2000]. However, asbestos clearly forms under very specific conditions of temperature and pressure from particular prerequisite starting materials. The infrequency with which these conditions and materials occur together accounts for the rarity of the asbestiform habit [Dorling and Zussman, 1987; Verkouteren and Wylie, 2000].

- Geology governs morphology [Wylie, 1999]. The asbestiform and nonasbestiform habit thus reflects their vastly different modes of origin. The asbestiform habit arises through unidirectional crystalline growth which produces exceedingly long, thin fibrils [NRC,1984]. Each fibril is therefore a single crystal. Individual asbestiform amphibole fibers, in turn, contain a relatively set number of fibrils that run parallel to one another. Asbestiform minerals are thus highly fibrous.

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[1] *Although the nonasbestiform and asbestiform habits of an amphibole mineral are nearly identical chemically,,* very subtle chemical differences may be important in determining growth habit. For example, the presence or absence of very small amounts of aluminum may determine whether an asbestiform or a nonasbestiform habit exists. [Verkouteren and Wylie, 2000; Dorling and Zussman, 1987; Deer, 1997]. The manner in which this is thought to influence habit is easy to explain. Thus, the very thin, long asbestos fiber is composed of highly aligned, almost perfected oriented chemical units all very tightly fitted together in one single direction. The atoms are, in fact placed into this linear structure so tightly that there is simply no room to accommodate an atom as large as aluminum. [Hodgson, 1986]. Substitutions of certain atoms with aluminum early in the formation of an amphibole mineral will thus lead to structural distortions that cause the development of prismatic crystals rather than asbestos fibers. [Hodgson, 1986]. The substitution of Al for Si increases the Z-O bond distances and therefore reduces the strength of bonding within and parallel to the length of the amphibole chains. *That* "very small amounts of AL can be effective is surprising." Dorling and Zussman [1987]. As stated above, this has been thought to occur mostly with aluminum but distortions in various sites have been thought to be due to calcium [Hodgson [1986], manganese [Hodgson, 1986], iron [Hodgson, 1986], titanium [Dorling and Zussman, 1987], chromium [Dorling and Zussman, 1987] as well.

Simple manipulation of asbestos can cause large numbers of very long, thin fibers and fibrils to split and be released [Verkouteren and Wylie, 2000; Langer and Nolan, 1991; Dorling and Zussman, 1987]. "Only specimens which occur as bundles of fibres (commonly having splayed ends) which readily split into still finer sub-microscopic units (fibrils), are referred to and are classed as asbestos" [Dorling and Zussman, 1987]. Thus, "fiber bundles are the hallmark of asbestos" Wylie [1999]

- Nonasbestiform amphiboles do not grow in the asbestiform habit. Their crystalline growth is not unidirectional; instead, it occurs along two or three planes. It gives rise to tiny "prisms" or irregularly shaped crystals by prismatic or acicular growth. Unlike asbestos, nonasbestiform amphibole minerals are not naturally fibrous and they are not naturally composed of fibers or fibrils. "The way a mineral sample breaks is determined by its crystal structure and geological history" … "You cannot make fibers out of non-fibrous material by mechanical manipulation" [Wylie, 1990]. Thus, nonasbestiform amphibole minerals never separate into fibers or fibrils. Instead, when nonasbestiform minerals are crushed, fragments are cleaved away from the main rock mass, a process that gives rise to "cleavage fragments." "Cleavage fragments were once part of a larger (non-fibrous) crystalline lattice which has been split apart due to the application of force" and therefore attain their shape by breakage, not by fibrous growth [Wylie, 1999].

- Surface properties are probably the most important factor distinguishing asbestiform from nonasbestiform amphibole fibers and reflect "differences in their origins" [Zoltai, 1979]. The geological forces that produce the asbestiform habit make the outer surfaces of asbestos fibers largely smooth and defect free [NRC, 1984; Hodgson, 1986; Zoltai, 1979; Walker, 1981; Dorling and Zussman, 1987; Lee and Fisher, 1979]. Each asbestiform fibril is a single crystal and its surface has "relatively well satisfied chemical bonds" [Walker, 1981]. "Cleavage fragments, on the other hand, have 'stressed' surfaces with less well satisfied bonds, surface irregularities, steps, and cracks and therefore have very different mechanical properties" [Walker, 1981], that include poor tensile strength and lack of flexibility.

- The surface of a cleavage fragment is created by external force, and consequently, is not expected to be as stable as (an asbestos fiber), since the stresses must have created a high density of surface defects and also cracks or incomplete fractures" [Zoltai, 1979]. "A strong surface structure with relatively few defects can develop only when the crystal grows in only one direction" NRC [1984] as is characteristic of asbestiform fibers (vs). Since the surfaces of asbestos fibers are "growth faces", not mechanical breakage planes, their surfaces are radically different from those of cleavage fragments. Electron microscopically, the "crystallographic orientation to an electron beam (of an asbestos fiber) differs markedly from the orientations of a cleavage fragment" [Langer and Nolan, 1991]. Macroscopically, "many asbestos fibers have the shiny luster and high

reflectivity indicative of a surface structure that is relatively free of defects" [NRC, 1984]. This is not the case for cleavage fragment derived materials.

- Strength and flexibility are the hallmarks of an asbestos fiber [NRC, 1984; Zoltai, 1979, 1981]. Such properties have enabled asbestos fibers to be exploited widely for the many commercial purposes they are uniquely suited to. The lack of defects in the outer surface of an asbestos fiber largely account for its great strength. Moreover, the outer surface needs to be stronger than its internal structure for a fiber to be flexible [Zoltai, 1979]. Thus, as each fiber is made up of a discrete number of fibrillar units, the greater outer surface strength of the fiber enables the fibrils within to "slide" past one another without causing the fiber to disintegrate. Their ability to slide past one another within the fiber enables the fiber to bend and therefore serves as the basis of its unique flexibility. Such sliding is also known as interplanar "parting" or "slip" and this occurs at sites called twinning planes [Wylie, 1999; Langer and Nolan, 1991; Hodgson, 1986; Zoltai, 1979]. Twinning planes, common in amphibole asbestos fibers, are very rare in nonasbestiform amphiboles and may be the main microstructural feature that differentiates the one from the other [Whittaker, 2000 pc; Wylie, 1999; Langer and Nolan, 1991].

- By contrast, weakness and inflexibility characterize a non – asbestiform fiber. The outer "surface (of a cleavage fragment) is thus weaker than its internal structure" [NRC, 1984]. "Cleavage cannot produce the high strength and flexibility of asbestiform fibers" NRC [1984]. "Individual asbestos fibers and cleavage fragments are strikingly different since the former are extremely strong and flexible, while cleavage fragments are weak and brittle [Zoltai, 1981]". Cleavage fragments "cannot be bent more than a few degrees" [NRC, 1984]. This makes "amphibole asbestos fibers more resistant to physical stress than the nonasbestiform varieties of the same mineral" [NRC, 1984]. Much of the observed variation in strength is due to differences in surface structure. The outer surface of a cleavage fragment is characterized by numerous defects and cracks that make it inherently weak and brittle. The defects and cracks are produced when external forces randomly tear away or break off portions of the nonasbestiform amphibole parent mineral's surface. The surface left behind will be jagged and full of defects. Not surprisingly, such surfaces are very weak. The inherent weakness is worsened by the fact that the "surface defects propagate brittle fracture", "the density of these defects (Griffith cracks) being inversely proportional to (the fiber's) tensile strength" [Hodgson, 1986]. Physical and chemical forces propagated along such superficial defects proceed internally to cause secondary structural faults and failure zones that weaken the already brittle cleavage fragment even further. [Wylie, 2000, pers com].

- Two additional pieces of evidence support the proposition that the outer surface of a cleavage fragment is weaker than its inner surface. The first comes from simple grinding studies. These demonstrate that cleavage fragments can easily be reduced to a powder by hand grinding [Verkouteren and Wylie, 2000; NRC, 1984] to yield short equant fragments [Dorling and Zussman, 1987; Langer and

Nolan, 1991]. By contrast, bundles of asbestiform amphibole fibers grind with great difficulty. This often causes the asbestos fibers to mat in the mortar [Verkouteren and Wylie, 2000; NRC, 1984; Dorling and Zussman, 1987] as they separate into their constituent fibrils [Dorling and Zussman, 1987]. The greater resistance of an asbestos fiber's surface to physical stress reflects the greater surface strength of the asbestiform over the nonasbestiform habit. The second piece of evidence to support the notion that a cleavage fragment's surface is weaker than its internal structure comes from dissolution studies. Thus, when soaked in acid, the dissolution of grunerite cleavage fragments begins on all surfaces. By contrast, the dissolution of asbestiform grunerite starts at the ends of the fibers and also requires a stronger acid to commence the dissolution process [Walker, 1981; NRC, 1984]. As dissolution proceeds, solid asbestiform fibers become partially hollow cylinders long before their surfaces have dissolved. By this time, many cleavage fragments have undergone complete dissolution [Walker, 1981; also see NRC, 1984; Zoltai, 1981]. The defect free outer surface of an amphibole asbestos fiber is highly acid resistant [Zoltai, 1981; Walker, 1981]. By contrast, the numerous cracks and defects on the surface of a cleavage fragment serve as "etch pits" that allow the acid to penetrate into the interior of the fiber, thus making it much less resistant to acid dissolution than an amphibole asbestos fiber [NRC, 1984; Walker, 1981;Zoltai, 1981,2000 pers.com.] Surface defects are "preferred sites for chemical attack" [Walker, 1981] through which fractures may be propagated. They further enhance the brittleness of the cleavage fragment [Hodgson, 1986; Wylie, 2000 pc] by weakening it along its entire length.

- The lack of surface strength so characteristic of cleavage fragments is reflected in their lack of tensile strength and flexibility. Macroscopically, the tensile strength of amphibole asbestiform fibers is between 20 to 115 times stronger than the nonasbestiform variety of the same amphibole mineral [NRC, 1984; Walker, 1981; Zoltai, 1981; Hodgson, 1965]. The difference in strength between asbestos fibers and cleavage fragments becomes greater as they get progressively thinner [NRC, 1984; Walker, 1981; Zoltai, 1981; Hodgson, 1965, 1986]. The difference is, moreover, probably greatest for fibers and fragments thin enough to meet the minimal width (< 0.5μm) and length (> 5u) criteria of a biologically relevant structure (vi). Asbestos fibers are unique since they display diameter - dependant strength. The thinner an asbestos fiber becomes, the stronger it gets [NRC, 1984; Zoltai, 1981; Walker, 1981]. Cleavage fragments do not display diameter dependant strength but become weaker as they get thinner [Zoltai, 1981; O'Hanley, 1986].

- The surface charge of asbestiform and nonasbestiform amphiboles also differ [Palekar et al, 1979; Zoltai, 1979]. Such differences may be biologically important since surface charge has been shown to be related to cationic exchange and particle absorption [Walker, 1981] as well as fibrogenic and tumorigenic potential [Davis et al, 1988; also see Hochella, 1993; Lee and Fisher, 1979; Brown et al, 1990].

The Differences in the Properties of Cleavage Fragments and Asbestos Fibers are Biologically Relevant.

Cleavage fragments do not possess the extreme dimensions of asbestos fibers:

- A very small proportion of cleavage fragments conform to the dimensions of asbestiform fibers. Even a smaller percentage of these ever resemble a structure longer than 5u and less than 0.5u in width. However, these cleavage fragments are not asbestiform fibers for, unlike asbestos, where the fibers and fibrils exist naturally in the mineral, cleavage fragment derived fiber-like structures only arise from nonasbestiform minerals by "accident" or by "cleavage fragmentation."

- Nonasbestiform amphiboles are exceedingly brittle and typically fracture horizontally to produce "short" cleavage fragments [Dorling and Zussman, 1987]. Asbestos fibers, however, don't typically break horizontally to produce short fibers when crushed. Instead, they tend to separate into fibrils of their original length [Dorling and Zussman, 1987]. Cleavage fragments tend to produce "chunks" that are, for the most part, much thicker than their asbestiform analogues. The random nature of cleavage fragmentation is therefore unable to generate uniformly long thin fibrils and fibers.

- Therefore, the fiber dimensional distributions of equivalent numbers of cleavage fragments and their asbestiform analogues differ greatly. Indeed, this is predictable on the basis of their vastly different modes of growth. Thus, as cleavage fragments get longer, their widths increase, so that nearly all that are longer than 5u are also greater than 0.3u in width [Chatfield, pers com.]. Thus, cleavage fragments thinner than 0.3 μm and longer than 15-20 μm are rare, if they exist at all. [Wylie et al, 1985]. By contrast, as asbestos fibers get longer, they remain uniformly thin [Wylie, 1987] so significant quantities of fibers longer than 5u and thinner than 0.1 u are formed. Berman et al. [1995] have also concluded that amongst asbestos fibers thinner than 0.3 μm, those longer than 40 μm are 500 times more potent than those shorter than 40 μm. Cleavage fragments of these dimensions do not exist.

- Cleavage fragments *cannot* form appreciable quantities of extremely long, thin "pathogenic" structures. Airborne dust composed of cleavage fragments contain very few long thin structures and the majority are not biologically relevant since, in addition to the features already discussed, they are too thick to be respired (ca < 2.5μm), too wide penetrate into the deep lung (ca < 0.6μm), or too thick to comport with a pathogenic width (ca < 0.15 - 0.3μm). The biological relevance of such width cut – offs to mesothelioma formation has been demonstrated by various researchers on the basis of epidemiological observations and attendant fiber size measurements made in air, ore, and lung tissue [e.g. Wylie et al, 1993: re Transvaal and Northwest Cape crocidolite; New York talc and Libby Montana verimiculite – tremolite, cummingtonite and grunerite cleavage fragments from

South Dakota and Minnesota; Karjalainenen et al, 1994; Karjalainenen, pers com, 1997 re Paakila Finnish anthophyllite; Shedd, 1985 re Western Australian, Cape and Transvaal crocidolites; Harrington et al, 1971, Timbrell et al, 1971, and Wagner, J C, pers com, 1999 re Transvaal and Cape crocidolites; Wagner et al, 1982 re: tremolite – anthophyllite cleavage fragment soil contamination Finland, Czechoslovakia, Yugoslavia, Bulgaria, Cyprus, Greece, and Turkey; Lippman, 2000]. Therefore, cleavage fragments cannot have the same carcinogenic potential as asbestos fibers since the vast majority do not conform to the structural dimensions that pose a mesothelioma risk.

Biopersistence strongly Determines Carcinogenicity and Cleavage fragments are far less Biopersistent than Asbestos fibers:

- Biopersistence strongly determines carcinogenicity and this appears to be largely macrophage - mediated. Macrophages can thus physically clear a fiber depending on its length and / or dissolve it depending largely upon its durability and surface strength.

The Ability of the Macrophage to Clear Asbestos and Nonasbestiform Cleavage Fragments is Very Different:

- Long, thin durable asbestiform amphibole fibers are the most difficult to clear and can easily "biopersist" long enough to produce severe adverse biological effects. The critical length for fiber clearance approximates the diameter of an alveolar macrophage [Lippmann, 2000] and is species – dependent [rat: 10-15u, Lippmann, 2000; 5-10u, Berman, 1995, 1999; 8u, Gil 1990; Valberg and Blanchard, 1991: humans: 10-15u, Berman, 1995, 1999; 24u, Gil 1990; Valberg and Blanchard, 1991; 17u, Timbrell, 1982, Musselman, 1994]. Gil [1990] and Valberg & Blanchard [1991] also believe human alveolar macrophages are better able to clear fibers than those of rodents due to their vastly greater surface areas and because the number of macrophages per alveolus (600 fold difference) in humans is much greater than in rodents. Since risk assessments generally ignore such comparative clearance considerations, they almost always overestimate human risks formulated solely on the basis of animal data.

- Long cleavage fragments are brittle and weak. They "cannot bend more than a few degrees" [NRC, 1984]. The severe physical stresses placed upon cleavage fragments as they enter, remain within, and/or leave the body are likely to cause them to break. Strong physical forces may be exerted on the fiber contained within the macrophage's cytoplasm. Alveolar collapse and expansion also impose tremendous bending forces causing them to break. The muscular strands of the macrophage's cytoskeleton may impose additional physical stresses during phagocytosis as the body of the macrophage changes shape and size. The macrophage thus becomes extremely attenuated as it enters lymphatic vessels and squeezes through tiny pores between epithelial cells.

- By contrast, asbestos fibers are extremely strong and flexible. "The relatively high flexibility of asbestiform fibers enables them to bend without breaking and may facilitate their passage through the respiratory tract" [NRC, 1984]. Direct measurements of tensile strength demonstrate that cleavage fragments are much weaker and less flexible than asbestos fibers of the same size [O'Hanley, 1986].

The Dissolution Properties of Asbestos and Nonasbestiform Cleavage Fragments are Very Different:

- Fibers thin enough to reach the deep alveolar lung are subject to "acid attack" as macrophages and other white cells release their acidic enzymes onto them. The exceedingly strong, defect free surface of an amphibole asbestos fiber confers upon it a very high level of acid resistance. Indeed, the unique ability of amphibole asbestos fibers to survive the harshest forms of chemical attack has formed the basis of many vital industries.

- Asbestos bodies are formed primarily upon long amphibole asbestos fibers. Acids can eventually cause amphibole asbestos fibers to break down particularly at "internodal" points along the length of the asbestos bodies since these areas are particularly weak and susceptible to breakage. Cleavage fragments are far weaker and less able than asbestos fibers to resist acid attack [NRC, 1984; Zoltai, 1981; Walker, 1981]. This causes them either to disintegrate completely or to break down at the internodal points along the length of the asbestos body. When this occurs, they become short enough to be phagocytosed and cleared from the body (vs).

- Finally, the difference in biopersistence between cleavage fragments and asbestos fibers may be most pronounced amongst the very small proportion of cleavage fragments with "biologically relevant" dimensions i.e. those longer than 5 μm and thinner than 0.5 μm. The explanation for this is that cleavage fragments become weaker as they become thinner. This follows from the fact that surface area is inversely related to diameter causing thin (e.g. 0.5μm or less) fibers to have very large surface areas. However, as the surface of an asbestos fiber is largely defect free, this enhancement of surface area does not significantly increase defect frequency. By contrast, the surface of a cleavage fragment contains many defects [Zoltai, 1981]. Therefore, as cleavage fragments become thinner, their surface area is increased and the number of surface defects therefore becomes very great [Zoltai, 1981]. Thus, thin cleavage fragments are far more susceptible to acid attack than amphibole asbestos fibers of the same width.

Animal Studies Demonstrate Cleavage Fragments are Not Carcinogenic:

- The effects of asbestos fibers and nonasbestiform cleavage fragments on animals have been assessed in the same studies to compare their carcinogenic potential. All such studies have used either intrapleural injection, intrapleural implantation, or intraperitoneal injection method. Each delivers massive doses directly to the mesothelium. This can only be accomplished by artificial exposure methods that bypass host defense mechanisms that normally prevent all but a small fraction of fibers from reaching the mesothelium following inhalation. Despite the extreme sensitivity of these injection test methods and the massive doses employed, cleavage fragments still fail to produce tumors or produce a tumor response that fails to exceed background [Ilgren 1989, 1991b,c]. By contrast, asbestos fibers in these injection studies produce high tumor rates not infrequently reaching 100%. The negative carcinogenic responses noted with cleavage fragments therefore provide very strong evidence that cleavage fragments are not carcinogenic to humans, particularly when the sensitivity of the assay and the large doses used are taken into consideration. The following summarizes the most relevant studies.

- ***Wagner et al [1982]*** intrapleurally injected rats with a 20 mg dose [102 million fibers longer than 5 μm, 41 million longer than 5u and less than 0.5 u wide] of tremolite [A] composed largely of nonasbestiform cleavage fragments [Nat'l Stone Assoc., 1990; Am. Mining Cong. 1990]. None of the rats developed mesotheliomas.

- ***Stanton et al [1981]*** intrapleurally implanted 40 mg. inocula of two talc tremolite cleavage fragment samples [6 and 7] in rats [also see Wylie Affidavit, 1984; Nat'l Stone Assoc., 1990]. The tumor rates did not exceed background.

- ***Smith et al [1979]*** intrapleurally injected hamsters with 10 and 25 mg doses of two tremolite cleavage fragment samples [275 and 14] [Nat. Stone Assoc., 1990; Am. Mine Cong., 1990]. Neither produced tumor rates that exceeded background.

- ***Davis et al [1991a]*** intraperitoneally injected rats with 10 mg. doses [49 million cleavage fragments longer than 5u; 2 million longer than 5μm and thinner than 0.5μm] of two tremolite cleavage fragment samples. The "Shinness tremolite sample", taken from a marble quarry, was analyzed electron microscopically and found to be "almost exclusively composed of very brittle cleavage fragments" [Addison, pers. com. 5/00; Davis et. al., 1991a]. The Shinness sample produced mesotheliomas in only 5.6% (2/36) of rats, an incidence well below background [Davis et al, 1991a,b.c]. The same number of asbestos fibers of similar dimensions would have produced a very high incidence of mesotheliomas (see Table 1 below) [Davis et al, 1991b]. Davis et al [1991b,c] said that asbestos fibers longer than 8 μm were the most carcinogenic in intraperitoneal injection studies. He stated further that "tumours may be expected regularly at dose levels of between 150,000 and 200,000 fibres (> 8u) and will develop in at least 25% of

animals if more than about 600,000 fibers are injected". However, the intraperitoneal injection of 17 million cleavage fragments longer than 8 μm [Davis et al, 1991b] failed to produce mesothelioma rates above background (Table 2 below). By contrast, much small numbers of asbestos fibers produced mesothelioma rates up to 95% (ibid). The second cleavage fragment sample from Dornie Scotland contained 24 million fibers longer than 5u and this also failed to produce tumor rates greater than background (data not shown). Davis et al [1991a] thus concluded that human exposure to materials such as those obtained from Shinness or Dornie, Scotland, whether as a pure mineral dust or as a contaminant of other products, "will almost certainly produce no hazard".

Table 1: Comparison of Shinness Tremolite "Fibers" (>5μm) and Asbestos Fibers (>5μm).

Type	Mass Dose	No. Fibers >5 μm Length	Meso. Incidence	Above Background?	Study
Shinness Tremolite (cleavage fragments)	10mg	49,000,000	5.6%	No	Davis et al [1991a]
Amosite	.05mg	1,700,000	25%	Yes	Davis et al [1991c]
Crocidolite	.05mg	2,075,000	25%	Yes	Davis et al [1991c]
Actinolite	.01mg	4,000,000	23%	Yes	Pott [1989]
Actinolite	.05mg	20,000,000	42%	Yes	Pott [1989]

Table 2: Comparison of Shiness Tremolite "Fibers" > 8μm and Asbestos Fibers > 8μm

Type	Mass Dose	#Fibers >8 μm Length	Meso. Incidence	Above Background	Study
Shinness(cleavage fragments)	10mg	17,000,000	5.6%	No	Davis et al [91a]
Amosite	2.5 mg	153,000	60%	Yes	Davis et al [88]
Amosite	0.05mg	305,000	28%	Yes	Davis [88]
Amosite	5.0 mg	305,000	78%	Yes	Davis [88]
Crocidolite	0.05 mg	420,000	25%	Yes	Davis [84]
Amosite	7.5 mg	458,000	65%	Yes	Davis [88]
Amosite	10 mg	610,000	72%	Yes	Davis [86]
Crocidolite	0.05mg	745,000	25%	Yes	Davis et al [91c]
Amosite	0.05mg	765,000	25%	Yes	Davis et al [91c]
Amosite	15mg	915,000	76%	Yes	Davis [88]
Crocidolite	0.5mg	4,200,000	31.3%	Yes	Davis [84]
Amosite	10mg	6,100,000	88%	Yes	Davis [84]
Amosite	25mg	1,525,000	95%	Yes	Davis [88]

In Vitro Studies:

- There have been at least three in vitro studies in which the biological effects of nonasbestiform cleavage fragments and asbestiform amphibole fibers were tested in the same study. Coffin and Palekar [1977] and Palekar et al [1979] assessed the effect of samples from the Homestake Gold mine in sheep erythrocyte hemolysis and rabbit alveolar macrophage cytotoxicity assays and found that the nonasbestiform amphiboles were generally ineffective in producing hemolysis and cytotoxicity whilst the asbestiform fibers were quite hemolytic and cytotoxic. Wagner et al [1982] assessed the effects of tremolite samples A and B (see above) on the release of LDH and BGL enzyme from mouse peritoneal macrophages; on giant cell formation in A549 cells; and on cytotoxicity to V79 cells. They found that neither sample was active in producing changes in these biological endpoints.

Epidemiological Studies Show No Association Between Exposure to Amphibole Cleavage Fragments and Asbestos Related Disease:

- To date, over 9,000 taconite, 3,000 gold, and 1,000 talc miners have been exposed to comparatively high concentrations of nonasbestiform amphibole cleavage fragments. Epidemiological studies of these workers have demonstrated no evidence of attributable asbestos related disease.

The Studies of the Homestake Gold Mine Workers:

- Steenland and Brown [1995] performed the most recent update of the Homestake gold mine cohort follow up [ave. 37 yrs.] ending in 1990. The study began in 1900 when pneumatic drilling commenced in underground pits. The analysis examined the patterns of mortality in miners [n = 3,328; 1,551 deaths] who had worked underground at the Homestake Gold Mine in South Dakota for at least one year between 1940-1965. The average duration of employment was 9 years. There were no deaths due to mesothelioma and there was no lung cancer excess [SMR 1.13]. The cohort had been exposed to significant levels of nonasbestiform amphibole [69% nonasbestiform cummingtonite-grunerite;[9] 15% nonasbestiform tremolite-actinolite; and 15% other nonasbestiform varieties]. "The geometric mean of personal exposures to fibers greater than 5 μm in length in the mid-1970's was 0.44 fibers/cm^3" when only 15% of the cohort was still employed [Steenland and Brown, 1995]. The dust levels prior to 1950 were at least several times higher than those found in the 1970s, suggesting that the average pre-1950 amphibole exposures were at least 2-3 fiber/cm^3 or higher. Using the data cited by Mc Donald et al [1978] (vi), the levels may have been ca. 45 fibers/cm^3. Since most [58%] of the cohort was employed before 1950, many men could have exposed to such increased levels. There were three earlier studies of the Homestake miners. Two [Brown et al, 1986; McDonald et al, 1978] also failed to find an association between nonasbestiform amphibole exposure and asbestos-related disease. The third [Gilliam et al, 1976] claimed an attributable excess mortality of malignant and non malignant respiratory disease but was based on inadequate follow-up and comparatively small numbers.

The Studies of the Minnesota Taconite Miners:

- The mining of taconite, as a major source of iron, began in the Mesabi range of Minnesota in the early 1950's. There have been three taconite mining operations in Minnesota and two of them have been the subject of detailed, long – term study. Both started operations before 1958. These studies were begun since concerns were raised in 1974 concerning possible adverse health related effects of nonasbestiform fibers found in the Duluth water supply. These triggered much regulatory, legal, environmental, and mineralogical activity.

- The first series of studies to investigate the health of the Taconite workers was based upon the Reserve Mining Company [RMC] work force. According to Cooper et al [1992], as the analyses of the RMC workers were negative for cancer, the American Iron Ore Association arranged for a second series of investigations to be done, this time of the Erie and Minntac Company situated immediately adjacent to the Reserve operations.

- Cooper et al [1992] did the latest update of the Minnesota taconite miners and millers [n = 3,444; 1,058 deaths] first exposed to taconite, silica, and nonasbestiform amphibole from 1947 to 1958. The minimum follow-up period from first exposure was 30 years and follow up was continued until 1988. According to Cooper et al [1992], "true asbestiform particles were very rare [at the mines], and most of the elongated particles were acicular (amphibole) cleavage fragments, principally grunerite and actinolite." No dust counts were available to permit quantitative estimates of past exposure to (nonasbestiform) particles. Cooper et al [1992] therefore relied on measurements of quartz as a method to "rank" dustiness. High exposure work categories thus included grinding, ore dressing, and palletizing. Using data cited by Higgins et al [1983] (vi), the levels to which the taconite miners and millers were exposed would probably have been consistent with those noted in the Homestake Gold mine studies. Higgins et al [1983] thus occasionally observed concentrations greater than 0.5 f/cc (>5u) but the concentrations were at least an order of magnitude higher than they would have been in earlier years. Cooper et al [1992] found one mesothelioma in the cohort but concluded it was not caused by exposures at the mine since exposures to taconite had begun only 11 years before his death. The relevant exposures were probably from work with boiler insulation on locomotives [Cooper et al, 1992]. There was no lung cancer excess [SMR < 100]. Cooper et al [1992] thus concluded that "The results are consistent with other epidemiological studies of the health effects of nonasbestiform amphiboles" that fail to show an association with asbestos related disease. Higgins et al's [1983] study of taconite miners [n = 5,751] employed between 1952 and 1976 also found no association between exposure to nonasbestiform amphibole and asbestos related disease.

The Studies of the New York State Talc Miners:

- Delzell et al [1995] conducted a retrospective follow-up of 818 talc miners and millers of the Gouverneur Talc Company [GTC] located in St. Lawrence County, New York. This was the latest in a series of studies of the GTC work force exposed to a tremolitic talc containing a high percentage of cleavage fragments. (see references cited in Delzell et al (1995) for earlier investigations). The study covered the years 1948 to 1989. The median follow up period was 21 years and the median duration of employment was 2 years. To date, there has been no evidence of attributable asbestos disease. Thus, a lung cancer excess was observed but was not felt to be attributable due to a lack of dose response and also

due to heavy exposures to cigarette smoke. Two mesotheliomas were also reported but both had potential asbestos exposures elsewhere.

The Study of the New York Hard Rock Tunnell Diggers:

- Selikoff [1978] studied 932 tunnel workers in New York City exposed from 1955 to 1972 to cleavage fragments from the massive, nonasbestiform amphibole, known as horneblende. There were 294 deaths but no evidence of asbestos related disease [Ross, 1982].

The Study of the Kennicott Copper Miners:

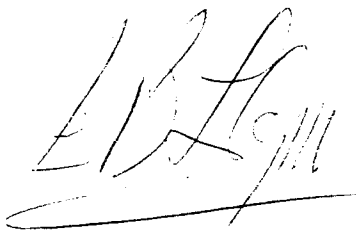
- The Kennicott Copper mine is one of the largest mining operations in the world. Workers have been exposed to cummingterite – tremolite cleavage fragments for many years [Hodgson, 1986] with no suggestion of attributable asbestos related disease [Kennicott management, 2000 pers com]

Conclusions

- Cleavage fragments are not asbestos ("nonasbestiform"). There are fundamental differences in the properties of cleavage fragments and asbestos fibers that clearly explain the observed differences in their carcinogenic potential. Cleavage fragments lack the strength, durability, flexibility and acid resistance of asbestos. They are therefore unable to persist in the body in a manner similar to asbestos.

- The scientific evidence demonstrates that cleavage fragments are noncarcinogenic in animals and humans. The methods used to assess tumor production in these animal studies are extremely sensitive and discriminatory even when the doses employed are vastly greater than any humans would encounter even under worst - case scenario exposure conditions. This is particularly relevant to allegations of low dose risk where the levels of exposure are exponentially lower than those employed in such animal studies. The fact that cleavage fragments are noncarcinogenic in such animal tests demonstrates that cleavage fragments, even at extremely high doses, do not pose a carcinogenic risk to humans. This conclusion is further supported by epidemiological studies performed on thousands of persons occupationally exposed to significant levels of cleavage fragments. Such studies demonstrate that no attributable risk, either for lung cancer or mesothelioma, exists from exposures to cleavage fragments.

E B Ilgren / 10 April 03.



APPENDICES

A. References

B. Curriculum Vitae of Dr. Ed Ilgren

C. List of Expert Testimony of Ed Ilgren (1998-2003)

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July, 1989 - Consultant
Present

July, 1997 - Honorary Member, Childhood Cancer Research Group, University of Oxford
Present

2002 – Consultant to the Strang Cancer Prevention Center, Cornell University Medical Center, New York City.

Degrees and Certifications

1974 Doctorate of Medicine, The Hahnemann Medical College, Philadelphia, Pennsylvania, USA.

1975 Diploma, National Board of Medical Examiners (USA).

1975 Licensure, Medicine and Surgery, State of New York, No. 124849.

1977 Board Certification, American Board of Pathology, Anatomic Pathology.

1980 Doctorate of Philosophy (Zoology / Botany), University of Oxford, Oxford, UK

1982 General Medical Council (United Kingdom), Full Registration.

1984 Master of Arts, (Status), degree conferred, University of Oxford, Oxford, UK

1998 Licensure, Medicine and Surgery, Commonwealth of Pennsylvania, No. 065102-L.

Fellowships and Grants

June, 1977 - Traveling Research Fellowship, International Union Against Cancer, ICRETT, Geneva,
July , 1977 Switzerland.

Oct., 1977 - Postdoctoral Research Fellowship, International Agency for Cancer Research / World Health
Jan., 1978 Organization, Lyon, France (Control of Trophoblastic Growth)

Jan., 1978 - Special Postdoctoral Research Fellowship, American Cancer Society, USA
Oct., 1979 (Control of Trophoblastic Growth)

Oct., 1979 - National Inst. Health Postdoctoral Training Award (Control of Trophoblastic Growth)
Sept., 1981

April, 1982 - Medical Research Council Project grant (Embryonic Regulation of Neural Neoplasia)
Sept. 1984

Sept., 1984 - Health & Safety Executive project grant: co-recipient with Prof P. Shubik,
July, 1985 (Iron Chelation: An attempt to develop a possible therapy for those at risk from exposure to asbestos by inhibiting formation, persistence, and effects of asbestos bodies *in vivo).*

Nov.1984 - Oxford District Research Grant Award (Embryonic regulation of neural neoplasia).
July 1985

Aug., 1985 - American Industrial Health Council Project Grant (Initiation and Promotion in Skin or
Nov. 1986 Liver Neoplasia: A 65 year annotated bibliography of international literature).

Aug. 1990 - W R Grace & Co. Research Project (Health Effects of Tremolite)
Sept. 1991

Memberships

St. Edmund Hall (Middle Common Room), Univ. Oxford	1976 - 1981
British Society Development Biologists (BSDB)	1979 - 1981
Tuberous Sclerosis Association (UK)	1981 - 1985
Neurofibromatosis Foundation (USA and UK)	1981 - 1985
Royal College of Pathology (Asso.)	1981 - present
British Society of Neuropathologists (BSN)	1981 - 1985
Neurosciences Specialty Group, University of Oxford	1981 - 1985
Oxford Proton Microprobe Group, Nuclear Physics, Univ. Oxford	1983 - 1985
British Medical Association (BMA)	1984 - 1986
International Fibre Safety Group (IFSG)	1990 - present
American Medical Association (AMA)	1992 - present
Pennsylvania Medical Society	1992 - present
Montgomery County Medical Society	1992 - present
International Commission on Occupational Health [ICOH]	1997 - present

Invited Lectures

1982	British Neuropathology Society (London) ("Prognostic Indices for Human Ependymomas")
1983	Ludwig Institute for Cancer Research, University of Bern ("Regulation of Neural Neoplasia")
1984	Faculty of Medicine, University of Lausanne ("Regulation of Neural Neoplasia")
1984	Institute for Brain Research, Zurich ("Elemental Mapping of the Human Brain")
1988	Swiss Neuropathology Society (St Moritz) ("Chronic Inflammation and Involvement of the Nucleus Ambiguus in MultiSystem Atrophy")
1989	Alfred P. Sloan Lecture, Bryn Mawr College ("Transplacental Initiation / Postnatal Promotion: Fetal Risk from Maternal Exposure")
1989	ICI (UK) - Central Toxicology Laboratory ("Complete Carcinogenesis: Ultraviolet Light and Chemical Carcinogens")
1989	ICI (Americas) - Wilmington, Delaware ("Initiation Irreversibility")
1989	Food and Drug Administration - Toxicology (Wash. D.C.) ("Initiation Irreversibility: Epidermal Studies")
1990	Food and Drug Administration - Toxicology (Wash. D.C.) ("Initiation Irreversibility: Non-Epidermal Studies")
1990	Eli Lilly - Central HQ, Ind., Ind. ("Carcinogenesis / Promotion Project")
1991	American College of Chest Physicians. Environmental Lung Disease. Fourth International conference. 25 - 28 Sept 1991 ("The potential health effects from low dose exposure to tremolite in vermiculite: An overview of the Libby, Enoree, and the Palabora experience".) (Montreal).
1991	International Congress of Occupational Health and Safety. (Montreal) 7 - 9 Sept 1991 ("Background mesotheliomas")
1991	Defense Research Institute, Asbestos Medicine Seminar (Scottsdale, Arizona) 20 - 23 Oct 1991 ("Mesothelioma threshold")
1992	Dow Chemical Company (Saginaw, Michigan) 12 July 1992 ("Mechanisms of Fibre related disease")
1992	International Agency for Research on Cancer, World Health Organization (Lyon, France), Biopersistence of mineral fibres ("Potential hypersusceptibility to the induction of mesotheliomas in hamsters exposed to ceramic fibres: theoretical biological mechanisms")
1993	Lead Industries Association (LIA) ("Lead and cancer") 11 October 1993, St Louis, Mo.